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Washington, D.C. 20231 on October 2, 2002

Doran R. Pace, Patent Attorney

RESPONSE UNDER 37 CFR §1.111

Examining Group 1634

Patent Application

Docket No. GJE-35

Serial No. 09/463,549

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Arun K. Chakrabarti, Ph.D.
Art Unit : 1634
Applicant : Daniel Henry Densham
Serial No. : 09/463,549
Filed : January 27, 2000
Conf. No. : 6468
For : Nucleic Acid Sequence Analysis

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Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE UNDER 37 CFR §1.111

Sir:

The remarks that follow are submitted for the Examiner's consideration in the above-referenced patent application in response to the Office Action dated August 8, 2002.

Remarks

Claims 1, 3-21, 30-34, 36, and 37 are pending in the subject application and currently before the Examiner. Applicant gratefully acknowledges the Examiner's indication that the previous rejections under 35 USC §112, second paragraph, have been withdrawn. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicant notes that the "Disposition of Claims" section on the Office Action Summary page indicates that claim 2 is pending in the subject application. For purposes of clarification only, it is noted that claim 2 was canceled by Applicant's Amendment dated November 20, 2001. The cancellation of claim 2 was acknowledged by the Examiner in the Office Action dated January 29, 2002.

Claims 1, 3-9, 21, 30-34, 36, and 37 are rejected under 35 USC §103(a) as obvious over Tsien *et al.* (WO 91/06678) in view of Holzrichter *et al.* (U.S. Patent No. 5,620,854) further in view of Seeger (U.S. Patent No. 5,360,714). In addition, claims are also rejected under 35 USC §103(a) as obvious over Tsien *et al.* (WO 91/06678) in view of Holzrichter *et al.* (U.S. Patent No. 5,620,854) further in view of Seeger (U.S. Patent No. 5,360,714) further in view of each of Schwarz *et al.* (1991), Chang *et al.* (U.S. Patent No. 5,801,042), O'Donnell (U.S. Patent No. 6,221,642), Rosenthal *et al.* (WO 93/21340), Vind (U.S. Patent No. 6,159,687), and Smith *et al.* (U.S. Patent No. 5,753,439). Applicant respectfully traverses each of these grounds of rejection.

Tsien *et al.*, Holzrichter *et al.*, and the Seeger patent are the primary combination of references used in all of the §103 rejections in the instant Office Action. The Tsien *et al.* reference is cited as the primary reference in each of the §103 rejections. However, as the Examiner acknowledges, the Tsien *et al.* reference does not teach or suggest the use of an immobilized polymerase. The Examiner relies on the Holzrichter *et al.* patent as teaching the use of an immobilized polymerase. The Examiner further indicates that the newly cited Seeger patent teaches "a nascent polynucleotide being synthesized as a result of the polymerase reaction wherein the complementary nucleotides are not labeled and the effect detected results from a conformation or mass change of the polymerase that occurs upon incorporation of the nucleotide."

In regard to the remaining secondary references, the Examiner asserts that the Schwarz *et al.* (1991) reference teaches the detection of nucleic acid incorporation by surface plasmon resonance

signal over time in the infra-red spectrum. The Examiner relies upon the Chang *et al.* patent for teaching a competitive inhibitor of the polymerase enzyme and the O'Donnell patent for teaching the beta-2 dimer complex of the *E. coli* DNA polymerase III with a target polynucleotide. The Examiner further asserts that the Rosenthal *et al.* reference teaches the Taq polymerase and that the Vind patent teaches reverse transcriptase as a polymerase. The Examiner cites the Smith *et al.* patent as teaching the detection of nucleotides by NMR using electromagnetic radiation.

Applicant respectfully asserts that the subject invention is not obvious over the newly cited combination of references. Applicant's claimed invention is based on Applicant's surprising discovery that the incorporation of a nucleotide into the reaction site of a polymerase during synthesis of a DNA strand complementary to the target DNA sequence results in an effect on the polymerase that can be detected by measuring radiation. The references cited in the instant Office Action, whether taken alone or in combination, do not teach or suggest the claimed invention. As Applicant indicated in the remarks submitted with the Preliminary Amendment dated June 28, 2002, the Tsien *et al.* reference, while disclosing a method for sequencing nucleic acids, only teaches the use of nucleotides that are "labeled" in some manner so as to be detectable in the nucleic acid strand being synthesized. In contrast, Applicant's claimed methods can be used with nucleotides that are not detectably labeled. The Holzrichter *et al.* patent relates to a general method for identifying biochemical and chemical reactions using a scanning probe positioned on or near a reaction site, which can then detect acoustic signals emitted directly from the reaction site or transmitted through a surrounding medium. In contrast to the Applicant's claimed method, which detects changes in, or absorption of, radiation from the polymerase/nucleotide/DNA reaction complex when nucleotide incorporation occurs, the Holzrichter *et al.* method detects acoustic signals or motions (vibrations) that result from a chemical reaction.

Turning to the newly cited Seeger patent, Applicant respectfully asserts that the disclosure in this patent does not cure the deficiencies of the other references cited by the Examiner. First, Applicant respectfully asserts that the disclosure in the Seeger patent relates to a synthesis method and not a sequencing method. The Seeger patent discloses the use of a polymerase enzyme, specifically a hepadnavirus polymerase gene product which possesses a DNA priming activity and a reverse transcriptase activity, to produce a nascent DNA strand from an RNA template, the product

of which can then be detected and quantified to determine the extent of the polymerase activity. However, the Seeger patent does not teach or suggest the identification or determination of any DNA or RNA sequence. Stated differently, if the template polynucleotide used in the polymerase reaction was unknown, the ordinarily skilled artisan would be unable to determine the sequence of the polynucleotide using the method described in the Seeger patent.

Applicant further asserts that there would be no motivation for an ordinarily skilled artisan to try and incorporate selected elements of the Seeger patent disclosure into a method for determining the sequence of a polynucleotide. Applicant respectfully asserts that an ordinarily skilled artisan would not have been motivated to substitute a nascent polynucleotide being synthesized as a result of the polymerase reaction of the Seeger patent into the DNA sequencing method the Examiner asserts is suggested by Tsien *et al.* combined with Holzrichter *et al.* Applicant respectfully asserts that since a nascent polynucleotide is synthesized in the method of Tsien *et al.*, there would be no reason to consider the teachings of the Seeger patent. Moreover, Applicant respectfully asserts that the express advantages of Seeger, as set forth by the Examiner, would not motivate an ordinarily skilled artisan to combine the cited references because the alleged ability of the Seeger method to provide for the “screening of many antiviral compounds” simultaneously and with rapidity has no relevance in regard to a method for determining the sequence of a DNA molecule.

As the Examiner is aware, it is well established in patent law that in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicant notes that currently pending claim 1 specifically recites that the detection of the effect consequent to nucleotide incorporation into a nascent polynucleotide is carried out by “measuring a change in, or absorption of, radiation that occurs if the nucleotide is incorporated.” (emphasis added) The Seeger patent does not teach or suggest measuring a change in, or absorption of, radiation. Claim 1 of the subject application also recites that detecting the effect consequent of nucleotide incorporation allows one to “thereby determine the sequence of the target polynucleotide.” There is nothing in the Seeger patent, nor in any of the other cited references, that teach or suggest that detection of an effect consequent to nucleotide incorporation into a nascent polynucleotide will allow

one to determine the sequence of the target polynucleotide. The Examiner has not cited any references that teach or suggest this element of Applicant's claimed invention. Thus, Applicant respectfully asserts that the combination of the Tsien *et al.*, Holzrichter *et al.*, and Seeger references, taken with or without the other secondary references, does not teach or suggest Applicant's claimed invention.

Moreover, Applicant also respectfully asserts that the result of the polymerase reaction of the Seeger patent is not determined on the basis of a conformational or mass change of the polymerase; there is no measurement or detection of a change in conformation or mass of the polymerase disclosed or suggested in the Seeger patent. Rather, the effect detected is simply the quantification of the amount of amplified DNA produced by the polymerase enzyme. The Examiner refers to the text at column 3, line 26, through to column 4, line 19, and column 16, lines 1-6, and claims 7, 16, and 18 of the Seeger patent as disclosing that the "effect detected results from a conformation or mass change of the polymerase" However, Applicant respectfully asserts that the teaching referred to by the Examiner is not present at the cited passages, or anywhere else in the Seeger patent. In fact, the Seeger patent specifically discloses at column 3, lines 41-44, that the effect detected is "... (4) detecting the **amount of the nascent DNA strand** in the separated complex, that amount being indicative of the reverse transcriptase activity of the hepadnavirus polymerase gene product." (emphasis added) Claims 7, 16, and 18 of the Seeger patent also recite that detection occurs by "... detecting the amount of said nascent DNA" Thus, Applicant respectfully asserts that there is no teaching or suggestion in the Seeger patent that is directed to measurement or detection of a change in conformation or mass of the polymerase upon incorporation of a nucleotide.

The Examiner acknowledges that the previously cited Tsien *et al.* and Holzrichter *et al.* references do not teach an ordinarily skilled person the invention as now claimed. The Examiner is relying on the Seeger patent, as a supplementary teaching, in an attempt to arrive at the claimed invention. However, as discussed in the preceding paragraphs, the Seeger patent does not correct the deficiencies in the primary references. Even if one assumes, *in arguendo*, that the Seeger patent did teach those elements lacking in the Tsien *et al.* and Holzrichter *et al.* references, Applicant respectfully asserts that the §103 rejections set forth in the instant Office Action rely on hindsight reconstruction in an attempt to select prior art references to try to suit or fit the limitations in the

claims. As the Examiner is undoubtedly aware, hindsight reconstruction of the prior art to arrive at Applicant's invention is not permissible. *In re Spinnoble*, 160 USPQ 237, 243 (CCPA 1969).

The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is, we must view the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 122 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

Applicant respectfully asserts that the references cited by the Examiner in the outstanding Office Action, for the reasons discussed herein, do not teach or suggest Applicant's claimed invention and, therefore, the claimed invention is not obvious over those references. Accordingly, reconsideration and withdrawal of all of the rejections under 35 USC §103(a) is respectfully requested.

In view of the foregoing remarks, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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